CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21057

CORRESPONDENCE

NDA 21-057

MAY 26 1999

Organon Inc.
Attention: Mr. Albert P. Mayo
Executive Director, Regulatory Affairs
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052

Dear Mr. Mayo:

Please refer to your pending January 28, 1999, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Antagon™ (ganirelix acetate) 250 µg, injection.

We are reviewing the Chemistry, Manufacturing and Quality Control section of your submission and have the following comments and information requests.

1. Please provide the following information:

   a. The reprocessing procedures that will be used when deviations from specifications occur during manufacturing,

   b. stability information for the drug product at 123°C for at least 25 minutes.

   c. the storage conditions and the stability of the working standard under the storage conditions,

   d. clarification as to whether tests were performed on the 15-month stability sample, and

   e. a list of samples that will be submitted for the methods validation.

2. The drug product specifications should be tightened for the related degradation products as noted below:

Degradation products	Specification (% declaration) Recommended limit
Org 14730	
Org 14733	
Org 14737	
Total	

In addition, please provide the following:

a. the USP method for bacterial endotoxin and sterility,

b. the upper limit of the extractable volume of the drug product in the specification, and

c. a description of the sampling plan for production batches for analyses.

3. The labeling should be revised as follows:

a. the Tradename should be added to the labeling,

b. the amount of mannitol present in the injection should be added to the **Each 0.5 ml syringe contains** section, and

c. the phrase,(/should be revised to read,/ in the labeling components, which include the syringe, blister pack, carton (box of 1), carton (box of 5) and carton (box of 50).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Ms. Diane Moore, Regulatory Project Manager at (301) 827-4260.

Sincerely,

/S/ 5/25/99

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for
Division of Reproductive and Urologic
Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-057
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/SSlaughter/SAllen/MRhee/SDe/TRumble
HFD-820/DNDC Division Director (only for CMC related issues)
DISTRICT OFFICE

Drafted by: dm/May 19, 1999/N21057CH

Concurrence:
TRumble 05.21.99/SDe, MRhee, MMann 05.24.99/LRarick 05.25

INFORMATION REQUEST (IR) /S/ 5/25/99

D. Moore

NDA 21-057

FEB - 3 1999

Organon Inc.
Attention: Mr. Albert P. Mayo
Executive Director, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Org 37462 (ganirelix acetate) Injection
Therapeutic Classification:	Priority (P)
Date of Application:	January 28, 1999
Date of Receipt:	January 29, 1999
Our Reference Number:	21-057

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 30, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 29, 1999.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 2/1/99

for Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-057
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/SSlaughter/RBennett/MRhee
HFD-580/AJordan/AParekh/LKammerman
DISTRICT OFFICE

/S/ 2/1/99

Drafted by: dm/February 1, 1999

filename: N21057AK.DOC

Concurrence:
TRumble 02.01.99

ACKNOWLEDGEMENT (AC)

AKZO NOBEL

Organon Inc.

July 29, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Revised Package Insert

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 29, 1999 telephone conference during which FDA requested additional revisions to the Antagon™ package insert.

We are herewith submitting the revised draft package insert for Antagon™: Attached please find the following items:

- Clean hard Copy of the revised draft package insert
- Electronic copy on one (1) diskette in WORD format.

If additional information is required or if there are any questions regarding the revised Antagon™ draft package insert, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

Organon

Attachments

Submitted in Duplicate via Federal Express Airbill No. 810494762586

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973)-325-4589

ORIGINAL CONFIDENTIAL

ORIG AMENDMENT

BL

AKZO NOBEL

Organon Inc.

July 23, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Revised Carton

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 19, 1999 telephone call, during which Ms. Diane Moore, of your Division, requested a revised copy of the Antagon™ carton based on FDA comments and to our July 19, 1999 telefax to FDA which included a hand revised copy of the carton.

We are herewith submitting a hard copy of the revised Antagon™ carton which incorporates text and graphic revisions as suggested in Ms. Moore's July 19, 1999 telephone conversation. The following items are attached:

1. Black and white version of the revised Antagon™ carton.
2. Laser color print copy of the revised Antagon™ carton. Please note that colors appear darker in this print than will actually appear on the carton. This is due to the nature of the laser printer used to generate the illustration.

Should you have any questions related to this correspondence, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier
for Albert P. Mayo
Executive Director
Regulatory Affairs

Organon

Attachments
FDA Form 356h

Submitted in duplicate
via Federal Express Airbill No. 810494763321

ORIGINAL

ORIG AMENDMENT

1 L

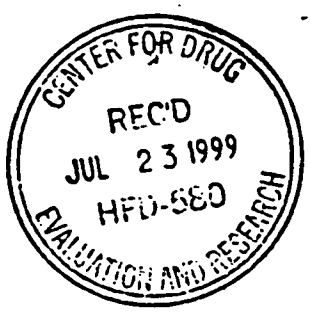
AKZO NOBEL

CONFIDENTIAL

Organon Inc.

July 22, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Package Insert

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 19, 1999 telephone call and to the July 21, 1999 telephone call and telefax from FDA during which Ms. Diane Moore of your Division requested the following revisions to the package insert:

1. Page 11, Line 225: Remove the word '
2. Page 10: Remove lines 203 - 207.
3. Page 10: Move lines 208 - 210 to the Pregnancy section as to read follows:

4. Page 8, Lines 168-171: Revise bullet item to read as follows:

Organon

Organon Inc.
5 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-0500
Fax: (973) 325-0594

CONFIDENTIAL

We are herewith submitting the revised draft package insert for Antagon™ including the above requested modifications with the exception that the suggested last sentence of Item 3. has been modified to read as follows:

Attached please find the following items:

- Clean hard Copy of the revised draft package insert
- Electronic copy on one (1) diskette in WORD format.

If additional information is required or if there are any questions regarding the revised Antagon™ draft package insert, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier

for Albert P. Mayo
Executive Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Attachments
FDA Form 356h

Submitted in Duplicate
via Federal Express Airbill No. 810494763332

ORIGINAL CONFIDENTIAL

AKZO NOBEL ORIG AMENDMENT

Organon Inc.

July 19, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Revised Carton

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 28, 1999. Reference is also made to the July 19, 1999 telephone call, during which Ms. Diane Moore, of your Division, requested a revised copy of the Antagon™ carton based on FDA comments.

We are herewith submitting a hand revised copy of the Antagon™ carton which incorporates text and graphic revisions as suggested in Ms. Moore's July 19, 1999 telephone conversation. Per Ms. Moore's request, this hand revised copy of the Antagon™ carton has been sent via telefax.

Changes to the carton are as follows:

1. The first line in the upper left corner which states has been revised to read:

2. The line running through and indenting the has been removed.

3. The line underlining has been removed.

Should you have any questions related to this correspondence, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier

for Albert P. Mayo
Executive Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Organon

Organon Inc.
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4589

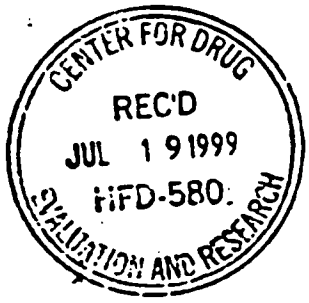
Submitted via telefax to Ms. Diane Moore: (301) 827-4267

ORIGINAL

ORIG AMENDMENT

AKZO NOBEL

Organon Inc.



July 19, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Revised Carton

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 28, 1999. Reference is also made to the July 16, 1999 telephone call, during which Ms. Diane Moore, of your Division, requested a copy of the Antagon™ carton.

We are herewith submitting a printed copy of the Antagon™ carton which incorporates text revisions as suggested in your May 26, 1999 correspondence regarding the Chemistry, Manufacturing and Control Section of our pending NDA. A copy of the carton has also been sent via telefax to Ms. Diane Moore.

Should you have any questions related to this correspondence, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier

for Albert P. Mayo
Executive Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Attachments
FDA Form 356h

Submitted in Duplicate
via Federal Express Airbill No. 810494763343

Submitted via telefax to Ms. Diane Moore: (301) 827-4267

Organon

Organon Inc.
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052
U.S.A.
T. (973) 325-4500
Fax (973)-325-4565

DUPLICATE CONFIDENTIAL

AKZO NOBEL ORIG AMENDMENT BC

Organon Inc.

July 12, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information : Drug Substance Eighteen Month Stability Report

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Antagon™ (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 8, 1999 telephone conference during which Dr. Swapan De requested that Organon submit the eighteen (18) month stability report on drug substance batch K which is used to produce the reference standard.

We are herewith submitting the requested stability report.

Please feel free to contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855 with nay questions you may have.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Attachments

Submitted in Duplicate
via Federal Express Airbill No. 810494762440

ORIGINAL

ORIG AMENDMENT

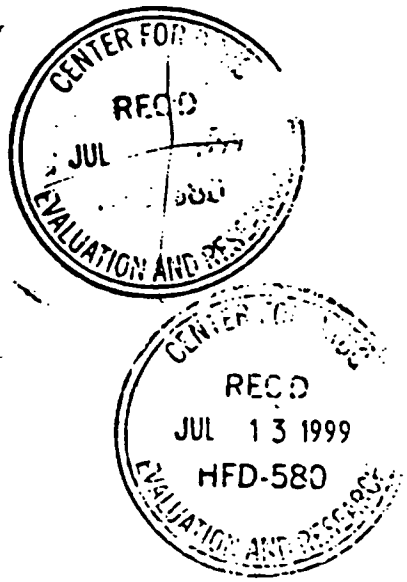
DV

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

July 11, 1999



Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Package Insert

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 9, 1999 telephone call from FDA during which Ms. Diane Moore of your Division requested that we add in Table I in the headings of columns 6 and 7 a "/F" and a note under Table I stating that F means "Absolute biolavailability".

We are herewith submitting the revised draft package insert (dated July 11, 1999) for Antagon™ with the requested modification. Attached please find the following items:

- Clean hard Copy of the revised draft package insert
- Electronic copy on one (1) diskette in WORD format.

In addition, as was relayed to Ms. Diane Moore of your Division and the NDA reviewing chemist, Dr. Swampan De, on Friday, July 9, 1999, Organon is accepting FDA's recommended specifications for degradation products as described in your May 26, 1999 correspondence to Organon.

Organon

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

If additional information is required or if there are any questions regarding the revised Antagon™ draft package insert, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

Attachments

Submitted in Duplicate
via Federal Express Airbill No. 810494762439

CONFIDENTIAL

AKZO NOBEL ORIGINAL

NEW CORRESP

Organon Inc.

NC

July 9, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Package Insert

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 8, 1999 telephone call from FDA during which Dr. Swapan De requested that we add the quantitative amount of glacial acetic acid (0.1mg) to the "description" section of the package insert.

We are herewith submitting the revised draft package insert (dated July 9, 1999) for Antagon™ with the requested modification. Attached please find the following items:

- Clean hard Copy of the revised draft package insert
- Electronic copy on one (1) diskette in WORD format.

Organon

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO IN: DATE

If additional information is required or if there are any questions regarding the revised Antagon™ draft package insert, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

Attachments

Submitted in Duplicate
via Federal Express Airbill No. 810429891661

BCC:

CA Cartier

ORIGINAL CONFIDENTIAL

AKZO NOBEL ORIG AMENDMENT

Organon Inc.

bv

July 8, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information - Package Insert

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the July 2, 1999 telephone call from Ms. Diane Moore of your Division, requesting minor changes to the package insert.

We are herewith submitting the revised draft package insert (dated July 6, 1999) for Antagon™ with the requested modifications. Attached please find the following items:

- Clean hard Copy of the revised draft package insert
- Electronic copy on one (1) diskette in WORD format.
- Discussion of how FDA' s comments were addressed

Organon

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CONFIDENTIAL

If additional information is required or if there are any questions regarding the revised Antagon™ draft package insert, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Albert P. Mayo

Albert P. Mayo
Executive Director
Regulatory Affairs

Attachments

Submitted in Duplicate
via Federal Express Airbill No. 808590822067

BCC:

CA Cartier

ORIGINAL

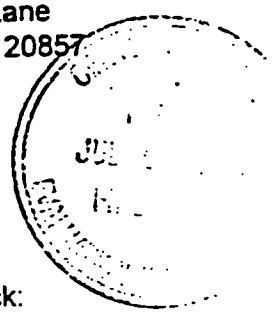
AKZO NOBEL ORG AMENDMENT

Organon Inc.

July 1, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL



NDA 21-057
Antagon™ (ganirelix acetate) Injection
REF: FDA Request for Information
Response to CMC Questions

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to your May 26, 1999 correspondence which included a request for information regarding the Chemistry, Manufacturing and Control Section of our pending NDA.

We are herewith submitting a written response to Chemistry, Manufacturing and Controls questions and are providing information as requested. Attached please find our response.

Please note that our response includes a listing of materials available for the validation package. We will submit samples and all associated documentation upon your request.

Should you have any questions related to this correspondence, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier

for Albert P. Mayo
Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ A.E. ☐ MEMO

CSO INITIALS DATE

Organon

Attachments
FDA Form 356h

Submitted in Duplicate
via Federal Express Airbill No. 810429891606

ORIGINAL CONFIDENTIAL

ORIG AMENDMENT

AKZO NOBEL

Organon Inc.

May 19, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Org 37462 (ganirelix acetate) Injection
REF: FDA Request for Information

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999. Reference is also made to the May 18, 1999 telephone call during which Ms. Diane Moore of your Division requested a copy of the Study 38613 subreport for metabolite profiling.

We are herewith submitting the requested subreport entitled:

> "An open-label study on the excretion balance and metabolite profile following a single intravenous injection of [^{14}C]-labeled Org 37462 in healthy female volunteers of reproductive age (clinical protocol 38613).
>
> Subreport on: Metabolite profiling in plasma, urine and feces samples form a mass balance study with [^{14}C]-Org 37462 (PBR-974473)."

If you require any additional information, please contact the undersigned at (973) 325-4833.

Sincerely,

for Albert P. Mayo
Executive Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Organon

Enclosures
FDA Form 356h

Sent in duplicate
via Federal Express Airbill No. 810429892668

AKZO NOBEL

ORIGINAL

ORIG AMENDMENT

50

Organon Inc.

April 27, 1999

CONFIDENTIAL

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

NDA No. 21-057
Org 37462 (ganirelix acetate) Injection
90-Day Safety Update

Dear Dr. Rarick:

Reference is made to our New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA No. 21-057 originally submitted on January 29, 1999.

We are herewith submitting an update of safety information related to Org 37462 in the form of a 90-day Safety Update. This 90-Day Safety Update is submitted as requested by Ms. Diane Moore, of your Division. The time period covered in this safety update is from September 1, 1998 to January 28, 1999.

Should you require additional information, please contact the undersigned at (973) 325-4833.

Sincerely,

Albert P. Mayo
Executive Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Organon

Attachments
Form FDA 356H

Archival Copy: Volumes 4.1 - 4.5
Clinical Copy: Volumes 4.1 - 4.5
Statistics Copy: Volumes 4.1 - 4.5

Submitted via Federal Express Airbill No. 810429893079

ORIGINAL

CONFIDENTIAL

NEW CORRESP

/VC

AKZO NOBEL

Organon Inc.

April 12, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B20
5600 Fishers Lane
Rockville, MD 20857

NDA 21-057
Org 37462 (ganirelix acetate) Injection
FDA Request for Information

Dear Dr. Rarick:

Please refer to our pending New Drug Application (NDA No. 21-057) for Org 37462 (ganirelix acetate) Injection. Please also refer to the March 19, 1999 telephone call from Dr. Krishan Raheja requesting justification for the dose selected for the Mouse Micronucleus Study.

We are attaching for your information, a response to Dr. Raheja from the Department of Toxicology & Drug Disposition at NV Organon, Oss, The Netherlands.

We are looking forward to a swift resolution of this issue.

Please feel free to contact me at (973) 325-4833.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

Attachments

Submitted in duplicate
via Federal Express Airbill No. 4101831274

Organon

ORIGINAL

ORIG AMENDMENT AKZO NOBEL

CONFIDENTIAL

Organon Inc.

March 29, 1999

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852 -1833

NDA 21-057
Org 37462 (ganirelix acetate) Injection
AMENDMENT TO PENDING NDA
REPLACEMENT PAGES

Dear Sir / Madam:

Reference is made to our January 29, 1999 New Drug Application NDA No. 21-057 for Org 37462 (ganirelix acetate) Injection. We have discovered that there are some inconsistencies in the tables of contents for the Chemistry, Manufacturing and Controls (CMC) information. In order to assure your efficient review we are herewith submitting replacement pages for the following tables of contents in specific NDA 21-057 volumes:

Volume No. / Subject		ITEM No.	Pages to Replace
Volume 1.1	CMC Tab	ITEM 1 Table of Contents	Page 0003
Volume 1.4	CMC	ITEM 4 Table of Contents	Pages 0001 & 0002
Volume 1.5	CMC	ITEM 4 Table of Contents	Page 0001
Volume 1.6	CMC	ITEM 4 Table of Contents	Page 0001
Volume 1.7	CMC	ITEM 4 Table of Contents	Page 0001
Volume 1.8	CMC	ITEM 4 Table of Contents	Page 0001
Volume 1.9	CMC	ITEM 4 Table of Contents	Pages 0001 & 0002

Should you have any questions or comments regarding this submission, please do not hesitate to contact the undersigned at (973) 325-4833.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Sincerely,

Albert P. Mayo
Executive Director, Regulatory Affairs

Attachments
Form FDA 356h

Sent in Duplicate via Federal Express Airbill No. 4101831440

Organon

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax. (973)-325-4589

CONFIDENTIAL

One (1) Desk Copy To:

Ms. Diane Moore, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

Sent via Federal Express Airbill No. 4101831451

One (1) Field Copy To:

Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902
Attention: Pre-Approval Coordinator

Sent via Federal Express Airbill No. 4101831436

ORIGINAL

AKZO NOBEL

NDA [redacted] Organon Inc.

February 23, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

REF: NDA 21-057, Org 37462 (ganirelix acetate) proposed proprietary name "Antagon"

Dear Dr. Rarick:

Please refer to our Original New Drug Application (NDA No. 21-057) for Org 37462 (ganirelix acetate) Injection which was submitted on January 29, 1999. Please also refer to your facsimile dated December 1, 1998 regarding the CDER Labeling and Nomenclature Committee recommendation to not accept the proposed proprietary name "Antagon" for Org 32462 (ganirelix acetate) Injection.

As stated in your December 1, 1998 facsimile, there was a concern that the proposed proprietary name "Antagon" would be misleading and inaccurate unless it antagonizes all gonadotropins. In addition, "Antagon" was rated as medium for potential to look-alike or sound-alike with another product "Anta-Gel". We herewith submit the following appeal to FDA's recommendation against the use of the name "Antagon".

> Gonadotropin releasing hormone (GnRH) is secreted from the hypothalamus. GnRH binds to the receptor on the pituitary gonadotroph and regulates the synthesis and secretion of gonadotropins, LH and FSH from the pituitary gland. Org 37462 Injection contains Org 37462 (ganirelix acetate), an antagonistic analog of GnRH as an active agent. In human clinical trials it has been very well established that administration of Org 37462 results in inhibition of both LH and FSH secretion. Org 37462 binds to the GnRH receptor on the pituitary gonadotroph and blocks the subsequent transduction pathways resulting in blockade of gonadotropins, LH and FSH secretion. Therefore, we strongly believe that the proposed proprietary name Antagon very accurately reflects the mode of action of Org 37462, i.e., antagonizes all pituitary gonadotropins and is not misleading. Org 37462 is administered subcutaneously.

Organon

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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"Anta-Gel" is a liquid antacid composed of alumina, magnesia and simethicone that is administered orally. "Anta-Gel" is manufactured by Pharmachemie, located in the Netherlands and does not appear to be currently marketed in the United States. It is not listed in the most recent edition of Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book).

We are confident that our proposed proprietary name "Antagon" accurately reflects the mode of action of Org 37462 and is not misleading. Further, the orally administered liquid antacid with the "look-alike/sound-alike" name "Anta-Gel" is intended for a treatment area far different from infertility. It is highly unlikely that circumstances will arise which can result in a mix-up of the drugs.

Should you have any questions, please contact the undersigned at (973) 325-4833 or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs

Sent via Federal Express Airbill No. 4101830434

ORIGINAL

CONFIDENTIAL

AKZO NOBEL

NEW CORRESPONDENCE Organon Inc.

February 9, 1999

Diane Moore, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857

NDA 21-057
Org 37462 (ganirelix acetate)
FDA Request for Information

Dear Ms. Moore:

Reference is made to our New Drug Application for Org 37462, NDA No. 21-057 submitted on January 29, 1999.

Per your request, please find the enclosed compact discs and floppy diskettes containing biopharmaceutics data in ASCII and Excel format for all pharmacokinetics studies included in the Org 37462 (ganirelix acetate) NDA No. 21-057.

ASCII data is contained on one compact disc and one floppy diskette. Excel worksheets are contained on one compact disc and one floppy diskette.

Should you have any questions or require further information, please contact the undersigned or Ms. Carole Ann Cartier at (973) 325-4855.

Sincerely,

for Carole Ann Cartier

Albert P. Mayo
Director
Regulatory Affairs

Attachments

Submitted via Federal Express Airbill No. 4101830294

Organon

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ N.A. ☐ MEMO

CSO INITIALS DATE

Organon Inc.
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ORIGINAL

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

NEW CORRESP

February 2, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-057
Org 37462 (ganirelix acetate) Injection
General Correspondence:
FDA Request for Information

Dear Dr. Rarick:

Please refer to our Original New Drug Application for Org 37462 (ganirelix acetate) Injection, NDA 21-057 submitted on January 29, 1999.

Per the request of Ms. Diane Moore of your Division, please find the enclosed copies of NDA Volumes to serve as desk copies. The following copies are enclosed:

1 copy	Volume 1.1	Application Fee Patent Information Claimed Exclusivity Debarment Certification Overall Index
2 Copies	Volume 1.51	Clinical Data Section
2 Copies	Volume 1.83	Integrated Summary of Effectiveness Data
2 Copies	Volume 1.84	Integrated Summary of Safety

If you require any additional information, please contact Carole Ann Cartier at (973) 325-4855.

Sincerely,

Carole Ann Cartier

for Albert P. Mayo
Executive Director
Regulatory Affairs

CENTER FOR DRUG
REC'D
FEB 0 3 1999
HFD-580
EVALUATION AND RESEARCH

Organon

Enclosures:
Desk copies (7)

REVIEWS COMPLETED
To: Diane Moore
CSO ACTION:
☒ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS DATE

Submitted via Federal Express Airbill No. 805407590788

Organon Inc.
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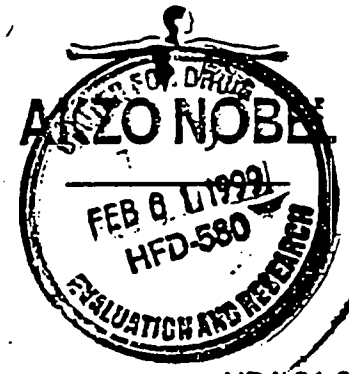

Organon Inc.

January 28, 1999

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852 -1833

NDA 21-057
Org 37462 (ganirelix acetate) Injection
ORIGINAL NEW DRUG APPLICATION

Dear Sir / Madam:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Organon Inc. submits herewith an original New Drug Application, Form 356h and supporting documentation for Org 37462 (ganirelix acetate) Injection.

Org 37462 is a novel GnRH antagonist, which modulates the hypothalamic-pituitary gonadal axis by competitively binding to the GnRH receptors in the pituitary gland. As a result a rapid, profound, reversible suppression of the release of pituitary gonadotropins (LH and FSH) occurs, without initial stimulation as observed with GnRH agonists. Org 37462 has been developed for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation (COH). Current practice in COH combines stimulation by exogenous gonadotropins with the suppression of endogenous gonadotropins by GnRH agonists. Use of agonists, however, gives rise to an initial flare-up of endogenous gonadotropin secretion and therefore requires a 2 to 3-week pre-treatment period to achieve complete suppression. In contrast, GnRH antagonists immediately (within only a few hours) suppress endogenous gonadotropins without initial stimulation and therefore require administration during only a short period of the stimulation, viz. when a premature LH surge is likely to occur. In the new Org 37462 regimen, controlled ovarian hyperstimulation with FSH usually starts at day 2 or 3 of menses. Daily subcutaneous administration of 0.25 mg Org 37462 is preferably started on day 6 of FSH administration. This daily treatment with Org 37462 should be continued up to the day that sufficient follicles of adequate size are present and final maturation of follicles may be induced.

Earlier antagonistic analogues of GnRH were known to cause hypersensitivity responses due to direct activation of mast cells resulting in the release of various mediators, in particular histamine. As a new chemical entity, the third-generation antagonist, Org 37462, was found to have significantly reduced histamine-releasing capacity in *in vitro* studies and was well tolerated by humans. Thus, hypersensitivity problems are not anticipated with this compound. Based on this positive profile for Org 37462 and the fact that there are currently no FDA-approved products for the prevention of LH surges in women undergoing controlled ovarian hyperstimulation, and as stated by Dr. Rarick during our October 28, 1996 meeting and as stated again by Ms. Diane Moore again during our September 9, 1998 teleconference, this NDA qualifies to receive a priority review and as a such **we hereby request a priority review for this NDA.**

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This application is intended to provide for the following indication for Org 37462 (ganirelix acetate) Injection:

1. The prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation (COH).

Please note that the above referenced NDA number has been pre-assigned. Org 37462 (ganirelix acetate) Injection has been investigated clinically under IND No. which resides with the Division of Reproductive and Urologic Drug Products. Please note that any and all data contained in IND No. are incorporated into NDA 21-057 by cross-reference.

Please note that submissions to IND have used the Organon code Org 37462 and the USAN / generic name ganirelix acetate. Following a request by Organon Inc. for the confirmation of the acceptability of the trade name "ANTAGON", FDA commented that the name would be unacceptable for use. Organon Inc. is in the process of appealing FDA'S rejection of the name "ANTAGON".

Please note that a categorical exclusion from the environmental assessment filing requirements is hereby claimed for this application in accordance with 21 CFR 25.31(b), as amended in the Federal Register 962 FR 40569), July 29, 1997.

In accordance with 21 CFR 314.50(k)(3), an identical field copy of the Chemistry, Manufacturing and Controls section of this NDA has been prepared for simultaneous submission to the FDA Newark District Office. Enclosed is a copy of the field copy transmittal letter and the signed certification that the copy submitted to the District Office is a true copy of that submitted to FDA headquarters.

On September 9, 1998, a teleconference was held between Ms. Diane Moore of FDA DRUDP and personnel from the Regulatory Affairs Department of Organon Inc. to discuss issues resulting from the September 9, 1998 FDA internal meeting regarding our June 26, 1997 submission of the Pre-NDA Information Package - Clinical Section (IND Amendment No. 073) and our August 26, 1997 submission of the remaining sections of the Pre-NDA Information package (IND Amendment No. 075). The following is a summary of pertinent points and agreements resulting from those interactions:

1. Historical Controls - As discussed during the October 28, 1996 meeting and during the September 9, 1998 teleconference, a review of historical data on the use of agonists versus nonuse would be performed. This review is included in the Integrated Summary of Efficacy.

2. Studies Supporting the Indication - FDA advised that this NDA can be submitted with the data of 2 European pivotal clinical studies. A US study is not required for submission of this NDA.

3. Batch Tolerance Information - FDA requested that batch profiles and tolerance information in the form of chromatograms of drug substance batches used in pre-clinical and clinical studies be included in this NDA.

4. Electronic Components - In addition to ASCII/SAS files, FDA agreed to receive Case Report Forms (CRF) and Tabulations for Studies 38602 and 38607 in electronic format according to the current FDA guidance document. FDA requested data listings and reports in paper form. Data listings can be included in the archival copy only.

5. Pre-NDA Meeting - It was agreed by both Organon Inc. and FDA to cancel the Pre-NDA Meeting scheduled for September 22, 1998 based on FDA acceptance of Organon's Pre-NDA Information Package resulting from their review and telephone discussions with Organon Inc.

6. Priority Review - FDA stated that the NDA is eligible to receive a priority review (review completed within six months).

As was presented to FDA in our pre-NDA information package dated August 26, 1998, and subsequently discussed during the September 9, 1998 teleconference, the clinical supplies and the intended market formulation contain the identical formulation and only differ in their final packaging (glass vials for the clinical supplies, pre-filled glass syringes for the intended product for market.) We thereby request a waiver from performing a bioavailabilitybioequivalence study.

Please note the cross-reference to the DMF for the ganirelix drug substance by They have not yet been assigned a DMF number but expect one shortly. We will relay this number to you when we receive it.

Please also note that this submission is in paper and electronic format. As agreed, the following data for the pivotal studies are provided in electronic format: Case Report Forms (CRFs) for dropouts (adverse events and deaths) and Case Report Tabulations (CRTs). In addition, all other case report forms for dropouts will be supplied electronically. Data listings for all completed studies are supplied in both paper and electronic format. All electronic data files will be provided on one CD-ROM. The file sizes are as follow: CRFs - 144MB, CRTs and Data Listings - 67MB. In addition the text of the Integrated Summary Documents and the Package

Insert are being provided in MS Word 7.0. The virus verification program used for these CDs is McAfee Virus Scan for Windows Version 3.1.1.

In addition, datasets in SAS format will be provided to FDA upon request following submission of this application.

We believe that the enclosed NDA is complete and organized to facilitate the ease of review. Therefore, review and evaluation at your earliest convenience would be greatly appreciated. Should you have any questions or comments regarding this submission, please do not hesitate to contact the undersigned at (973) 325-4833.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Sincerely,

Albert P. Mayo

Albert P. Mayo
Executive Director, Regulatory Affairs